

***Amendment and Response***

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*Serial No.: 10/028,224**Confirmation No.: 4497**Filed: 21 December 2001**For: CRYSTALLIZATION AND STRUCTURE DETERMINATION OF GLYCOSYLATED HUMAN BETA  
SECRETASE, AN ENZYME IMPLICATED IN ALZHEIMER'S DISEASE***Remarks**

The Office Action mailed 17 March 2004 has been received and reviewed. Claims 1-53 and 77-78, which are drawn to non-elected groups, have been canceled herein. Applicants reserve the right to prosecute the canceled claims in continuation and/or divisional applications. New claims 79-107 having been added, the pending claims are 54-76 and 79-107.

The new claims are generally supported by the specification and originally filed claims. Specifically, new claims 79-82, 84-85, 88-89, 94, 96, 98, and 100 are supported, for example, by Figure 1. New claims 83, 86-87, 90, 93, 95, 97, and 99 are supported by the specification at, for example, page 45, line 22 to page 47, line 5; and page 47, lines 11-12. New claims 91-92 are supported by the specification at, for example, page 12, line 24 to page 13, line 8. New claims 101-107 are supported, for example, by originally filed claims 54-67 and the specification at, for example, page 14, lines 1-23; page 17, line 4 (reciting "substrates"), and page 45, line 22 to page 47, line 5.

Reconsideration and withdrawal of the rejections are respectfully requested in view of the remarks presented herein.

**Copending Application**

Applicants directed the Examiner's attention to copending application Serial No. 10/027,277 in the Information Disclosure Statement mailed March 1, 2002. Applicants also wish to draw the Examiner's attention to the Office Actions mailed September 8, 2003 and July 26, 2004, and the rejections recited therein, for copending application Serial No. 10/027,277.

**Provisional Statutory-Type Double Patenting Rejection**

Claims 54-76 were provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 1-23 of copending Application Serial No. 10/027,277. Claims 54, 56, and 72-76 were provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 4, 5, and 24-28 of copending Application Serial No. 10/144,441.

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Since the statutory-type double patenting rejections are provisional, Applicants respectfully defer responding to the provisional rejections until the Examiner has indicated otherwise allowable subject matter in claims 54-76, at which time Applicants will provide appropriate responses.

**Provisional Obviousness-Type Double Patenting Rejection**

Claims 54, 55, and 57-71 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 6-23 of copending Application Serial No. 10/144,441. Claims 54-69 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-23 of co-pending U.S. Application No. 10/143,502. Claims 54-67 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-26 of co-pending U.S. Application No. 10/143,723.

Since the obviousness-type double patenting rejections are provisional, Applicants respectfully defer responding to the provisional rejections until the Examiner has indicated otherwise allowable subject matter in claims 54-69, at which time Applicants will provide appropriate responses.

**Rejections under 35 U.S.C. §112, First Paragraph****Written Description**

The Examiner rejected claims 54-76 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection.

"To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." M.P.E.P. §2163(I). "An applicant may . . .

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show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." M.P.E.P. §2163(II)(A)(3)(a).

Applicants thank the Examiner for acknowledging that the specification provides an adequate written description for species of methods and crystals that include human beta secretase of SEQ ID NO:1 and the inhibitor of Figure 1; and crystals having the trigonal space group symmetry  $P3_221$  and unit cell dimensions of  $a = b = 112 \pm 20 \text{ \AA}$ ,  $c = 110 \pm 20 \text{ \AA}$ ,  $\alpha = \beta = 90^\circ$ , and  $\gamma = 120^\circ$  (paragraph spanning pages 3 and 4 of the Office Action mailed March 17, 2004). The Examiner's attention is drawn to new claims 83, 86, and 93-96, which recite beta secretase having amino acid sequence SEQ ID NO:1; new claims 80, 82, 85, 89, 94, 96, 98, and 100, which recite the inhibitor of Figure 1; and new claims 83-85, 87-89, 93-94, and 97-98, which recite a crystal having the trigonal space group symmetry  $P3_221$  and comprising a unit cell having dimensions of  $a$ ,  $b$ , and  $c$ , wherein  $a = b = 112 \pm 20 \text{ \AA}$ ,  $c = 110 \pm 20 \text{ \AA}$ ,  $\alpha = \beta = 90^\circ$ , and  $\gamma = 120^\circ$ .

However, the Examiner described the issue at hand as whether a species (e.g., a species of beta secretase and/or a species of inhibitor) is sufficient to represent an entire genus. Applicants traverse the rejection for at least the reasons recited in the traverse in the Amendment and Response submitted February 12, 2004, which are incorporated herein by reference. Further, although M.P.E.P. §2163 states that "[t]he claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art," Applicants respectfully submit that suitable species of beta secretase and suitable species of inhibitors are described in the specification, and that additional species are conventional and known to one of ordinary skill in the art.

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Specifically, Applicants respectfully submit that in view of the present specification, one of skill in the art would recognize that additional species of beta secretases and additional species of inhibitors could be used in methods and crystals of the present invention.

*First*, Applicants respectfully submit that the Examiner has acknowledged that other species of human beta secretase are known to one of skill in the art (e.g., page 5, first paragraph of the Office Action mailed March 17, 2004), and the present specification even provides methods for determining structural homology of other species of human beta secretase (e.g., page 25, line 24 to page 26, line 28). Thus, Applicants respectfully submit that the disclosure of SEQ ID NO:1, in view of the teachings of the present specification, fully support the claimed genus of beta secretase crystals and methods.

*Second*, Applicants respectfully submit that the Examiner has acknowledged that other species of beta secretase inhibitors are known to one of skill in the art, as evidenced, for example, by Chopra et al., Hong et al., Tang et al., and Beyer et al. Thus, Applicants respectfully submit that the disclosure of the inhibitor illustrated in Figure 1, in view of the teachings of the present specification and the knowledge of one of skill in the art, fully support the claimed genus of beta secretase crystals and methods.

*Additionally*, the Examiner noted that the hypothetical claim recited in the Trilateral Project WM4 on *Comparative study on "protein 3-dimensional (3-D) structure related claims* (i.e., "A crystalline form of protein P having unit cell dimensions of  $a=4.0\text{nm}$ ,  $b=7.8\text{nm}$ , and  $c=11.0\text{nm}$ ") recites specific unit cell dimensions. Applicants respectfully submit that due to routine variations that occur in the determination of unit cell dimensions, Applicants are entitled to claim a reasonable range of dimensions to adequately protect their presently disclosed invention. Nonetheless, the Examiner's attention is directed to new claims 86 and 90, which do not recite a range of unit cell dimensions.

*Finally*, the Examiner noted that the unit cell dimensions in claims 73 and 74 are not required to be equivalent. Applicants respectfully submit that it would be obvious to one of skill

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in the art that for trigonal space groups,  $a = b$ , and that no correction is required. Nonetheless, the Examiner's attention is drawn to new claims 83-90 and 93-100, which recite that  $a = b$ .

For at least the reasons presented herein above, Applicants respectfully submit that the specification provides sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention, thus satisfying the written description requirement under 35 U.S.C. §112, first paragraph.

*Enablement*

The Examiner rejected claims 54-76 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse the rejection.

"A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." M.P.E.P. §2164.04. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied."

M.P.E.P. §2164.01(b). "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be *used* in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not *use* the genus as a whole without undue experimentation." M.P.E.P. §2164.02, paragraph entitled "WORKING

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EXAMPLES AND A CLAIMED GENUS" (emphasis added). "[E]ven in unpredictable arts, a disclosure of every operable species is not required." M.P.E.P. §2164.03.

Applicants thank the Examiner for acknowledging that the specification provides adequate enablement for species of methods and crystals that include human beta secretase of SEQ ID NO:1 and the inhibitor of Figure 1; and crystals having the trigonal space group symmetry  $P3_221$  and unit cell dimensions of  $a = b = 112 \pm 20 \text{ \AA}$ ,  $c = 110 \pm 20 \text{ \AA}$ ,  $\alpha = \beta = 90^\circ$ , and  $\gamma = 120^\circ$  (last paragraph of page 6 of the Office Action mailed March 17, 2004). The Examiner's attention is drawn to new claims 83, 86, and 93-96, which recite beta secretase having amino acid sequence SEQ ID NO:1; new claims 80, 82, 85, 89, 94, 96, 98, and 100, which recite the inhibitor of Figure 1; and new claims 83-85, 87-89, 93-94, and 97-98, which recite a crystal having the trigonal space group symmetry  $P3_221$  and comprising a unit cell having dimensions of  $a$ ,  $b$ , and  $c$ , wherein  $a = b = 112 \pm 20 \text{ \AA}$ ,  $c = 110 \pm 20 \text{ \AA}$ ,  $\alpha = \beta = 90^\circ$ , and  $\gamma = 120^\circ$ .

However, the Examiner described the issue at hand as whether the specification enables the entire scope of the claimed crystals and methods. Applicants traverse the rejection for at least the reasons recited in the traverse in the Amendment and Response submitted February 12, 2004, which are incorporated herein by reference. However, the Examiner appears to have attempted to rebut Applicants' arguments by assertions of high degree of unpredictability and undue experimentation (e.g., page 10, last paragraph of the Office Action mailed March 17, 2004). Although the Examiner has attempted to support his assertions by citing Chopra et al., Tang et al., and Hong et al. Applicants respectfully traverse the rejection.

Applicants acknowledge that the Examiner has made a showing that the type of beta secretase crystal grown may depend on the pH used in the crystallization method. Applicants also note that present claims 54-71 recite methods for crystallizing human beta secretase *at a pH different than the pH reported by Chopra et al., Hong et al., or Tang et al.*

In response to Applicants arguments, the Examiner noted that the formation of crystals at a pH range of 3.5 to 5.5 is not recited in claims 72-76. Applicants respectfully note that claims 72-76 are directed to crystals *per se*, and thus, do not recite method conditions (e.g., pH

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conditions) for making a crystal. Moreover, claims 72 and 74-76 recite the *space group P3<sub>1</sub>21*, which differs from space groups I222 (e.g., reported by Chopra et al.), P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> (e.g., reported by Tang et al.), and P2<sub>1</sub> (e.g., reported by Hong et al.) Further, claim 73 recites *unit cell dimensions* (e.g.,  $\gamma=120^\circ$ ) that are inconsistent with the space groups I222 (e.g., reported by Chopra et al.), P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> (e.g., reported by Tang et al.), and P2<sub>1</sub> (e.g., reported by Hong et al.). Thus, Applicants' Representatives do not understand the intent of the Examiner's statement. In the event that the rejection is maintained, Applicants invite the Examiner to clarify the statement in the next Official Communication.

The Examiner also asserted that "replacement of methionine with selenomethionine in a given protein alters the amino acid and chemical composition of the protein. Thus, when crystallized, such homologs, splice variants, and selenomethionine mutants may pack differently forming different crystals from that of the protein of SEQ ID NO:1, even under identical crystallization conditions (page 12, lines 17-20 of the Office Action mailed August 12, 2003). In response, Applicants asserted that one of skill in the art would not necessarily expect replacement of a methionine with selenomethionine to result in different packing properties. Replacement of methionine by selenomethionine is well known in the art of protein crystallography as a method of incorporating heavy atoms into a molecule to aid in the solution of the x-ray crystal structure for the native molecule (e.g., without selenomethionine), and that the technique is useful *specifically* because the incorporation of the heavy atoms does not substantially disrupt the crystal structure, and cited Hendrickson et al. for support.

In response to Applicants' arguments, the Examiner noted that Hendrickson et al. do not address the crystallization of selenomethionyl beta secretase (page 9, last paragraph of the Office Action mailed March 17, 2004). Applicants respectfully submit that perhaps the Examiner did not understand the intent of Applicants' arguments. To clarify Applicants arguments, Hendrickson et al. was cited by Applicants as exemplary support for the well known technique used by one of skill in the art to aid in solving protein crystal structures, by incorporating heavy elements (e.g., selenium) into the protein. Thus, Applicants respectfully submit that one of skill

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in the art would have a reasonable expectation of crystallizing a protein (e.g., a beta secretase) having selenomethionine incorporated therein without substantially disrupting the crystal structure of the native protein (e.g., a beta secretase). Applicants respectfully submit that the Examiner's notation that Hendrickson et al. do not address the crystallization of selenomethionyl beta secretase fails to rebut Applicants' argument.

Further, as exemplary support for Applicants assertion that one of skill in the art, using the disclosure provided in the specification (including the working examples), would be able to make and use the entire scope of the claimed invention, Applicants' Representatives recited the use of the presently disclosed crystals in cross-seeding techniques. Applicants note that the Examiner indicated that Applicants' arguments were not persuasive, and cited *In re Wands*. However, Applicants respectfully submit that the Examiner has failed to specifically rebut the arguments (e.g., including cross-seeding techniques) presented by Applicants.

Thus, for at least the reasons presented herein above, Applicants respectfully submit that the full scope of the present claims is enabled by the specification.

Based on the remarks presented herein above, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §112, first paragraph.

**New Claims**

Language of new claims 80, 82-90, and 93-100 has been noted and discussed herein above. Applicants respectfully submit that new claims 80, 82-90, and 93-100 are patentable for at least the reasons presented herein above for the patentability of claims 54-76.

New claims 79 and 81 depend from claims 75 and 76. Applicants respectfully submit that new claims 79 and 81 are patentable for at least the reasons presented herein above for the patentability of claims 75 and 76.

New claims 91 and 92 recite crystals of beta secretase having atoms arranged in a spatial relationship represented by the structure coordinates listed in Table 1 or Table 3. Applicants



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respectfully submit that claims 91 and 92 are patentable at least for the reasons presented herein above for the patentability of, for example, claims 72-76.

New claims 101-107 recite methods for crystallizing human beta secretase. Applicants respectfully submit that new claims 101-107 are patentable for at least the reasons recited herein above for the patentability of claims 54-71.

Entry and consideration of new claims 79-107 is respectfully requested.

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Summary

It is respectfully submitted that all the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for  
Timothy E. BENSON et al.

By  
Mueeting, Raasch & Gebhardt, P.A.  
P.O. Box 581415  
Minneapolis, MN 55458-1415  
Phone: (612) 305-1220  
Facsimile: (612) 305-1228  
Customer Number 26813

Date

September 17, 2004By: 

Loren D. Albin

Reg. No. 37,763

Direct Dial (612)305-1225

CERTIFICATE UNDER 37 CFR §1.8:

The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 17<sup>th</sup> day of SEPTEMBER, 2004, at 4:15 PM (Central Time).

By: Name: SAM HER